# Factors influencing the prognosis of patients with intrahepatic cholangiocarcinoma

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## Abstract

***Background and aims :*** **The outcome of surgical treatment of patients with intrahepatic cholangiocarcinoma (ICC) is poor. This study was designed to analyze prognostic factors following surgical treatment for ICC.**

***Patients and methods :*** **A structured telephone interview was conducted in 132 patients who were surgically treated for ICC. Fifteen clinical and pathological factors that may influence post-operative survival were analyzed by using Cox proportional hazards model.**

***Results :*** **The accumulative 1-, 3-, 5-year survival rate of the 132 patients was 51.3%, 21.6%, and 11.8% respectively. The mean survival time in patients with elevated serum carbohydrate antigen (CA) 19-9 at the time of the operation was shorter than in patients with normal serum CA19-9 (9.6 ± 24.7 vs 16.1 ± 6 months, $P < 0.01$). The median survival time in patients with well-differentiated carcinoma was longer than in those with poorly differentiated ICC (23.9 ± 7.8 vs. 11.2 ± 5.0 months, $P < 0.01$). Patients who were treated with hepatectomy and lymph node dissection had a longer survival time than those treated with hepatectomy only (16.0 ± 5.8 vs 10.2 ± 3.6 months, $P < 0.01$). Multivariate analysis showed that mode of surgical treatment, lymph node metastasis, serum level of CA 19-9 and pathological differentiation grade of ICC predicted postoperative survival.**

***Conclusions :*** **Hepatectomy with lymph node dissection is associated with an improved survival for patients with ICC. This strategy may be recommended for the surgical treatment of ICC.**
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**Key words** : intrahepatic cholangiocarcinoma ; hepatectomy ; lymph node metastasis ; mortality ; prognosis.

## Introduction

Intrahepatic cholangiocarcinoma (ICC) is a relatively uncommon cancer of the bile ducts, arising from malignant transformation of the epithelial cells that line the biliary apparatus (1). The incidence of ICC is on the increase in the past two decades (2). No standard treatment has been established so far, but liver resection or hepatectomy and adjuvant chemotherapy or radiotherapies have been used to treat ICC (1-5). Although surgical resection of ICC may be potentially curative (1), the five-year post-operative survival rate is below 50% and the recurrence rates remain high (2-7). Several studies have attempted to elucidate the predicting factors for post-operational survival in patients ICC, and most of the studies found that lymphatic metastasis and histological grade were related to the prognosis of the patients (8-10). Patient's old age, high preoperative carbohydrate antigen 19-9 (CA19-9) level, and narrow ICC resection margin also predicted poor clinical outcomes (11). To date, hepatectomy appears to be the only effective surgical technique for ICC, and the role of lymph node dissection is unclear. In a small study on 64 patients, lymph node dissection did not affect the survival in the patients without lymph node involvement, but it enhanced the survival in patients with lymph node metastasis (10). Overall, the evidence supporting the use of lymph node dissection is scarce, and the role of routine hilar lymphadenectomy is considered controversial (1). In this study, we analyzed the clinical outcomes of 132 ICC patients who underwent hepatectomy and lymphatic dissection, and described the factors predicting post-operational survival with a particular emphasis on lymphatic dissection.

## Patients and Methods

### *Patient selection*

This study was approved by the Human Research Ethics Committee of Liaocheng People's Hospital. Informed written consent was obtained from all study participants or the relatives. Patients admitted to Liaocheng People's Hospital from December 1996 to July 2003 for surgical treatment of ICC were selected. There were 112 males and 71 females, with a mean age of 53.2 years (Table 1). Before surgery, hepatic ultrasonography and CT scan were performed in all patients. MRI scan was also performed in 59 patients to confirm diagnosis. Laboratory tests included viral hepatitis B surface antigen (HBsAg), serum alpha fetoprotein (AFP), carcinoembryonic antigen and cancer antigen19-9 (CA 19-9). The diagnosis and staging of ICC was based on the American Joint Committee on Cancer (AJCC) 7th edition staging manual (12).

### *Follow up*

Patients were followed up bi-monthly at our hospital clinics after the surgery. More frequent follow up was

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conducted in patients who received post-operative radiotherapy or chemotherapy. For the purpose of this study, a structured telephone interview was conducted by the investigators between February and June 2005 to all patients who received surgical treatment. For the deceased patients who had surgeries before the interview, the pre-death details were provided by their families or relatives. This one-off interview covered issues such as post-surgical re-admissions, pharmacological or radiotherapies, and recurrence of the cancer.

*Statistical analysis*

Statistical analysis was performed using SPSS, version 13.0. Data were expressed as mean ± SD, or percentages where appropriate. Fifteen clinical and pathological factors that could possibly influence survival were selected. These factors were age, sex, blood transfusion, intrahepatic metastasis, surgery, adjuvant therapy, lymph node metastasis, tumor size, envelope, histology, AFP, CA19-9, total bilirubin level (TBIL), serum albumin and globulin ratio (A/G) and cirrhosis. A multivariate analysis of these factors was performed using a Cox proportional hazards model. *P* values less than 0.05 were considered significant.

## Results

*General findings*

As shown in Table 1, 14 patients were asymptomatic at the time of the surgery, and diagnosis was based on hepatic ultrasound examination and CT scans. HbsAg, alpha fetoprotein and carcinoembryonic antigen were found in a small proportion of patients. CA19-9 was detected in more than half of the patients.

The surgical procedures performed were listed in Table 2. One hundred and fifty nine (74.9%) of the patients were treated with curative hepatectomy, 46 (25.1%) of them were also treated with lymph node dissection. Among the 24 (13.1%) patients treated with palliative operation, 9 received local hepatectomy and lymph nodes of hepatic hilar region. Duodenohepatic ligament was marked with silver clip in order to receive postoperation radiotherapy. Two patients (1.1%) received liquid nitrogen frozen therapy, and three (1.6%) received post-operative chemotherapy. Local excision of the tumor was performed in 6 patients (3.3%) with lymph node metastasis of the lesser omentum and in 4 patients (2.2%) with lymph node metastasis around the head of the pancreas. Diagnosis was confirmed in the 183 patients based on pathological examination following the surgery, and the types of cancer are listed in Table 3.

Table 1. — **Clinical characteristics of the 183 patients**

| Age (yrs) | Average 53.2 (*range*, 25-79) |
|---|---|
| Male | 112 (61.2%) |
| Clinical manifestation | |
| Asymptomatic | 14 (7.7%) |
| Symptomatic | |
| Abdominal discomfort | 105 (57.4%) |
| Fatigue | 38 (20.8%) |
| Infantile | 17 (9.3%) |
| Hepatomegaly | 9 (4.9%) |
| Associated liver disease | |
| Hepatolithiasis | 27 (14.8%) |
| Schistosomiasis | 9 (4.9%) |
| Hepatitis B surface antigen | 42 (23.0%) |
| Alpha fetoprotein | 49 (26.7%) |
| Carcinoembryonic antigen | 11 (6.0%) |
| Cancer antigen19-9 | 109 (59.6%) |

Table 2. — **Surgical procedures of the 183 patients**

| Surgical procedures | Number |
|---|---|
| Laparotomy | 13 (7.1%) |
| Palliative operation | 24 (13.1%) |
| Curative operation | |
| left three lobectomy | 5 (2.7%) |
| right three lobectomy | 7 (3.8%) |
| mist-lobectomy | 21 (11.5%) |
| left external lobectomy | 23 (12.6%) |
| right posterior lobectomy | 18 (9.8%) |
| caudate lobotomy | 4 (2.2%) |
| local hepatectomy | 41 (22.4%) |
| lymph node dissection | 46 (25.1%) |

Table 3. — **Macroscopic types and histopathological types in the 183 patients**

| | Types | Number of patients |
|---|---|---|
| Macroscopic types | Mass-forming type | 65 (35.5%) |
| | Periductal-infiltrating type | 71 (38.8%) |
| | Intraductal growth type | 47 (25.7%) |
| Histopathological types | Well-differentiated | 52 (28.4%) |
| | Moderately differentiated | 89 (48.6%) |
| | Poorly differentiated | 42 (23.0%) |

*Follow up and survival analysis*

Patients or their relatives were contactable in 132 (72.1%) of the 183 cases in 2005. The remaining patients were either not contactable or unwilling to participate in the follow up studies. In the 132 patients who completed telephone interviews, 34 patients (25.8%) underwent post-operative transcatheter hepatic arterial chemoembolization (TACE) (1-3 times), 11 (8.3%) received percutaneous ethanol injection therapy, 17 (12.9%) received radiotherapy, 12 (9.1%) received routine chemotherapy, and 3 (2.3%) received cryomachimes.

Of the 132 cases, 74 (56.1%) are still alive at the time of the interview. Fifty-eight patients (43.9%) died of cancer recurrence or metastasis. The average survival time was 13.8 months. The 1, 3 and 5-year survival rate was 51.3%, 21.6% and 11.8%, respectively. Fifty-eight patients (43.9%) had elevated serum CA19-9 at the time of the operation, and the survival time in these patients was shorter than in patients with normal serum CA19-9 ($9.6 \pm 24.7$ vs. $16.1 \pm 6$ months, $P < 0.01$). Eleven patients with serum CA19-9 level above 1000U/ml died

Table 4. — **Predicting factors for post-operational mortality in 132 patients who completed follow up**

| Factors | Coefficient of regression | WALD$\chi^2$ | *P* value | Relative risk |
|---|---|---|---|---|
| Lymph node metastasis | 1.297 | 11.532 | 0.001 | 3.896 |
| Curative surgical procedure | -1.456 | 4.026 | 0.043 | 0.298 |
| Pathological differentiation | 0.689 | 11.681 | 0.001 | 1.654 |
| Serum level of CA19-9 | 2.315 | 6.743 | 0.032 | 2.236 |

within one year. The median survival time of well-differentiated, moderately differentiated and poorly differentiated carcinoma was 23.9 ± 7.8, 19.1 ± 6.4 and 11.2 ± 5.0 months, respectively ($P < 0.01$). Forty-six patients (34.9%) received curative hepatectomy and lymph node dissections, and the postoperative survival time in these patients was a longer than that of patients underwent hepatectomy alone (16.0 ± 5.8 vs 10.2 ± 3.6 months, $P < 0.01$).

Cox stepwise regression analysis showed that non-curative surgical procedure, presence of lymph node metastasis, serum level of CA19-9 ≥ 37 U/ml and a poor pathological differentiation grade were independently correlated with low post-operative survival (Table 5). Blood transfusion, postoperative radiotherapy or chemotherapy, diameter of tumor, serum level of alpha-fetoprotein, cirrhosis, preoperative total serum bilirubin level, ratio of albumin to globulin, sex and age were not predicting factors for postoperative survival.

## Discussion

Although majority of previous research had confirmed that surgery was an important treatment for ICC, the post-operative survival rates of ICC are still low (1). Pathological findings revealed that intrahepatic metastasis near the main lesion was common in mass-forming type ICC, and recurrence was seen in the adjacent liver tissue (1). In the present study, 89.6% of tumors were not enveloped, intrahepatic metastasis was found in 29.7% of the specimens, and most patients did not develop severe cirrhosis. Multivariable analysis indicated that there was significant correlation between surgical treatment and prognosis. In line with other studies (13,14), we also found that extensive hepatectomy improves the prognosis of patients without lymph node metastasis.

Lymph node metastasis is believed to be an important factor for postoperative prognosis, and some studies suggested that systematic lymph node dissection could improve the outcome of ICC patients (15,16). One study even involved extrahepatic bile duct resection combined with vessel and/or pancreas resection (17). Compared with conventional surgery, which was defined as hepatectomy alone or hepatectomy with bile duct resection, the extended surgery did not improve the curative resection rate or the surgical outcome for ICC, and a significantly higher mortality rate was observed after extended surgery (1). In the present study, the mean survival time in patients treated with lymph node dissections and hepatectomy was 6 months longer than patients treated with hepatectomy alone, suggesting that lymph node dissections and hepatectomy is associated with a better survival outcome.

Our study also found that serum CA19-9 level was related to patient prognosis. Patients with elevated serum CA19-9 levels at the time of the operation had a shorter survival time than in patients with normal CA19-9. Moreover, patients with serum CA19-9 level above 1000 U/ml did not survive for more than 12 months. This study also found that pathological grades of the cancer were correlated with the prognosis. The median survival time of well-differentiated, differentiated carcinoma was 9 months longer than the poorly differentiated carcinoma. These results are in line with a recent report where tumor differentiation was found to be an independent prognostic factor for disease-free survival (10).

In conclusion, major hepatectomy with systematic lymph node dissection may be recommended for the surgical treatment of ICC. This treatment strategy is associated with an improved survival for ICC.

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